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THERAPEUTIC COMBINATIONS OF ANTIHYPERTENSIVE AND ANTIANGIOGENIC AGENTS

Abstract:

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The invention concerns the use of a combination of an anti-angiogenic agent and an anti-hypertensive agent for use in the manufacture of a medicament for the treatment of a disease state associated with angiogenesis in a warm-blooded mammal, such as a human being. The invention also relates to pharmaceutical compositions comprising an anti-angiogenic agent and an anti-hypertensive agent, to kits thereof and to a method of treatment of a disease state associated with angiogenesis which comprises the administration of an effective amount of a combination of an anti-angiogenic agent and an anti-hypertensive agent to a warm-blooded animal, such as a human being. Data supplied from the esp@cenet database - Worldwide

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(54) Title: THERAPEUTIC COMBINATIONS OF ANTIHYPERTENSIVE AND ANTIANGIOGENIC AGENTS

(57) Abstract: The invention concerns the use of a combination of an anti-angiogenic agent and an anti-hypertensive agent for use in the manufacture of a medicament for the treatment of a disease state associated with angiogenesis in a warm-blooded mammal, such as a human being. The invention also relates to pharmaceutical compositions comprising an anti-angiogenic agent and an anti-hypertensive agent, to kits thereof and to a method of treatment of a disease state associated with angiogenesis which comprises the administration of an effective amount of a combination of an anti-angiogenic agent and an anti-hypertensive agent to a warm-blooded animal, such as a human being.



WO 01/74360 A1

THERAPEUTIC COMBINATIONS OF ANTIHYPERTENSIVE AND ANTIANGIOGENIC AGENTS

The present invention relates to a method for the treatment of a disease state associated with angiogenesis by the administration of an anti-angiogenic agent and an anti-hypertensive agent, to a pharmaceutical composition comprising an anti-angiogenic agent and an anti-hypertensive agent, to a kit comprising an anti-angiogenic agent and an anti-hypertensive agent, and to the use of an anti-angiogenic agent and an anti-hypertensive agent in the manufacture of a medicament for use in the production of an anti-angiogenic effect in warm-blooded animals, such as humans.

Angiogenesis, the process of forming new blood vessels, plays an important role in a variety of normal processes including embryonic development, wound healing and several components of female reproductive function. However, undesirable or pathological angiogenesis has been associated with a number of disease states including diabetic retinopathy, psoriasis, cancer, rheumatoid arthritis, atheroma, Kaposi's sarcoma and haemangioma (Fan et al, 1995, Trends Pharmacol. Sci. 16: 57-66; Folkman, 1995, Nature Medicine 1: 27-31).

Angiogenesis is stimulated via the promotion of the growth of endothelial cells. Several polypeptides with *in vitro* endothelial cell growth promoting activity have been identified including, acidic and basic fibroblast growth factors (aFGF & bFGF) and vascular endothelial growth factor (VEGF). The growth factor activity of VEGF, in contrast to that of the FGFs, is relatively specific towards endothelial cells, by virtue of the restricted expression of its receptors. Recent evidence indicates that VEGF is an important stimulator of both normal and pathological angiogenesis (Jakeman et al, 1993, Endocrinology, 133: 848-859; Kolch et al, 1995, Breast Cancer Research and Treatment, 36:139-155) and vascular permeability (Connolly et al, 1989, J. Biol. Chem. 264: 20017-20024). Alteration of vascular permeability is also thought to play a role in both normal and pathological physiological processes (Cullinan-Bove et al, 1993, Endocrinology 133: 829-837; Senger et al, 1993, Cancer and Metastasis Reviews, 12: 303-324).

Thus antagonism of the activity of VEGF is expected to be beneficial in a number of disease states, associated with angiogenesis and/or increased vascular permeability, such as cancer, diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and

chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, excessive scar formation and adhesions, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation. For example, antagonism of VEGF action by sequestration of VEGF with antibody can result in inhibition of tumour growth (Kim et al, 1993, Nature 362: 841-844).

VEGF binds to a receptor with intrinsic tyrosine kinase activity, a so-called receptor tyrosine kinase (RTK). RTKs are important in the transmission of biochemical signals across the plasma membrane of cells. These transmembrane molecules characteristically consist of an extracellular ligand-binding domain connected through a segment in the plasma membrane to an intracellular tyrosine kinase domain. Binding of ligand to the receptor results in stimulation of the receptor-associated tyrosine kinase activity which leads to phosphorylation of tyrosine residues on both the receptor and other intracellular molecules. These changes in tyrosine phosphorylation initiate a signalling cascade leading to a variety of cellular responses. To date, at least nineteen distinct RTK subfamilies, defined by amino acid sequence homology, have been identified. One of these subfamilies is presently comprised by the *fms*-like tyrosine kinase receptor, Flt or Flt1, the kinase insert domain-containing receptor, KDR (also referred to as Flk-1), and another *fms*-like tyrosine kinase receptor, Flt4. Two of these related RTKs, Flt and KDR, have been shown to bind VEGF with high affinity (De-Vries et al, 1992, Science 255: 989-991; Terman et al, 1992, Biochem. Biophys. Res. Comm. 1992, 187: 1579-1586). Binding of VEGF to these receptors expressed in heterologous cells has been associated with changes in the tyrosine phosphorylation status of cellular proteins and calcium fluxes.

Compounds which are inhibitors of VEGF receptor tyrosine kinase are described, for example in, International Patent Applications Publication Nos. WO 97/22596, WO 97/30035, WO 97/32856, WO 97/34876, WO 97/42187, WO 98/13354, WO 98/13350, WO 99/10349, WO 00/21955 and WO 00/47212.

In the normal mammal blood pressure is strictly controlled. This is facilitated by a complex interaction of a number of mediators, whose effects are maintained at an equilibrium. The system is such that if the level of one mediator changes this is compensated for by the other mediators such that normal blood pressure is maintained. (for a review of the systems which maintain blood pressure the reader is referred to: Guyton et al 1972 Annual

Review of Physiology 34, 13-46; and Quan et al 1997 Pacing and Clinical Electrophysiology 20, 764-774). It is important that blood pressure is tightly controlled because hypertension, high blood pressure, underlies a variety of cardiovascular diseases, such as stroke, acute myocardial infarction, and renal failure.

5 A number of substances exhibit effects on blood vessels *in vitro* which in isolation would suggest effects on blood pressure *in vivo*. However, because of the nature of the control of blood pressure often any effects *in vivo* are compensated for and thus normal blood pressure is maintained.

 It has been reported that VEGF and FGF have acute effects on vascular tone. VEGF
10 has been shown to dilate coronary arteries in the dog *in vitro* (Ku et. al., 1993, Am J Physiol 265:H585-H592) and to induce hypotension in the conscious rat (Yang et. al., 1996, J Cardiovasc Pharmacol 27:838-844). However, *in vivo* these effects are only transitory. Even with a very large dose of VEGF (250µg/kg) in conscious rats Yang et al observed a return to normal blood pressure within 20 minutes, at lower doses blood pressure returned to
15 normal significantly faster. Boussairi et. al. have observed a similar effect upon administration of bFGF to anaesthetised rats, with the blood pressure returning to normal within 30 minutes after addition of 15µg/kg bFGF (J Cardiovasc Pharmacol 1994 23:99-102). These studies also show that tachyphylaxis (or desensitisation) quickly develops following growth factor administration. Thus further administration of growth factor has no
20 effect on blood pressure.

 It has been reported that the vasodilation induced by both FGF and VEGF depends, at least in part, on the release of nitric oxide (NO), also referred to as endothelially derived relaxant factor (EDRF), (Morbidelli et. al., 1996, Am J Physiol 270:H411-H415 and Wu et. al., 1996, Am J Physiol 271:H1087-H1093).

25 In International Patent Application Publication No. WO 98/28006 a method for treating a hypertensive disorder in a pregnant woman is described, the method comprising administering to the pregnant woman an amount of a therapeutic substance which regulates the amount, and/or activity of, VEGF. In International Patent Application Publication No. WO 00/13703 is described a method for treating hypertension comprising administering to a
30 patient an effective amount of an angiogenic factor such as VEGF, or an agonist thereof.

Whilst administration of high levels of VEGF to conscious rats only produces a transient decrease in blood pressure, which cannot be maintained due to tachyphylaxis, we have found surprisingly that a VEGF receptor tyrosine kinase inhibitor leads to a sustained increase in blood pressure in rats when administered more than once, particularly when
5 administered chronically. Thus the present invention relates to ways in which an antiangiogenic effect may be produced in a warm-blooded animal, such as a human being, without causing hypertension.

Thus according to the present invention there is provided a method of treatment of a disease state associated with angiogenesis which comprises the administration of an effective
10 amount of a combination of an anti-angiogenic agent and an anti-hypertensive agent to a warm-blooded animal, such as a human being.

According to a further feature of the present invention there is provided the use of a combination of an anti-angiogenic agent and an anti-hypertensive agent for use in the manufacture of a medicament for the treatment of a disease state associated with
15 angiogenesis in a warm-blooded mammal, such as a human being.

According to a further feature of the present invention there is provided a pharmaceutical composition comprising an anti-angiogenic agent and an anti-hypertensive agent for the treatment of a disease state associated with angiogenesis in a warm-blooded mammal, such as a human being.

20 According to a further aspect of the present invention there is provided a method for producing an anti-angiogenic and/or vascular permeability reducing effect in a warm-blooded animal, such as a human being, which comprises administering to said animal an effective amount of a combination of an anti-angiogenic agent and an anti-hypertensive agent.

25 According to a further aspect of the present invention there is provided the use of a combination of an anti-angiogenic agent and an anti-hypertensive agent for the manufacture of a medicament for producing an anti-angiogenic and/or vascular permeability reducing effect in a warm-blooded mammal, such as a human being.

According to a further aspect of the present invention there is provide a
30 pharmaceutical composition, comprising an anti-angiogenic agent and an anti-hypertensive

agent, for producing an anti-angiogenic and/or vascular permeability reducing effect in a warm-blood mammal, such as a human being.

According to a further aspect of the present invention there is provided a pharmaceutical composition, comprising:

- 5 a) an anti-angiogenic agent or a pharmaceutically acceptable salt, solvate or pro-drug thereof;
- b) an anti-hypertensive agent or a pharmaceutically acceptable salt, solvate or pro-drug thereof; and optionally
- c) a pharmaceutically acceptable carrier or diluent.

10 According to a further aspect of the present invention there is provided a method for treating a warm-blooded animal such as a human being, in need of an anti-angiogenic effect comprising administering to said animal:

- a) an amount of a first compound, said first compound being an anti-angiogenic agent or a pharmaceutically acceptable salt, solvate or prodrug thereof or a pharmaceutical
- 15 composition thereof; and
- b) an amount of a second compound, said second compound being an anti-hypertensive agent or a pharmaceutically acceptable salt, solvate or prodrug thereof or a pharmaceutical composition thereof;

wherein said first compound and said second compound are either administered together or
20 are administered sequentially with either compound administered first.

According to a further aspect of the present invention there is provided a kit, for use in producing an anti-angiogenic effect and/or vascular permeability reducing effect in a warm-blooded animal such as a human being, comprising:

- a) an anti-angiogenic agent or a pharmaceutically acceptable salt, solvate or pro-drug thereof
- 25 or a pharmaceutical composition thereof;
- b) an anti-hypertensive or a pharmaceutically acceptable salt, solvate or pro-drug thereof or a pharmaceutical composition thereof; and
- c) a container means for containing said agents.

As discussed above it is believed that the vasodilation induced by VEGF and FGF is
30 dependent on nitric oxide. Thus, without being bound by theoretical considerations it is

believed that the increase in blood pressure induced by a VEGF inhibitor is dependent on modulation of nitric oxide levels.

Thus according to a further aspect of the present invention there is provided a method of treatment of a disease state associated with angiogenesis which comprises the
5 administration of an effective amount of a combination of an anti-angiogenic agent, which affects the level of nitric oxide, and an anti-hypertensive agent to a warm-blooded animal, such as a human being.

According to a further feature of the invention there is provided the use of a combination of an anti-angiogenic agent, which affects the level of nitric oxide, and an
10 anti-hypertensive agent for use in the manufacture of a medicament for the treatment of a disease state associated with angiogenesis in a warm-blooded mammal, such as a human being.

According to a further feature of the invention there is provided a pharmaceutical composition comprising a combination of an anti-angiogenic agent, which affects the level
15 of nitric oxide, and an anti-hypertensive agent for the treatment of a disease state associated with angiogenesis in a warm-blooded mammal, such as a human being.

According to a further aspect of the present invention there is provided a method of treatment of a disease state associated with angiogenesis which comprises the administration of an effective amount of a combination of an anti-angiogenic agent, which blocks the
20 signalling of a tyrosine kinase, and an anti-hypertensive agent to a warm-blooded animal, such as a human being.

According to a further feature of the invention there is provided the use of a combination of an anti-angiogenic agent, which blocks the signalling of a tyrosine kinase, and an anti-hypertensive agent for use in the manufacture of a medicament for the treatment
25 of a disease state associated with angiogenesis in a warm-blooded mammal, such as a human being.

According to a further feature of the invention there is provided a pharmaceutical composition comprising a combination of an anti-angiogenic agent, which blocks the signalling of a tyrosine kinase, and an anti-hypertensive agent for the treatment of a disease
30 state associated with angiogenesis in a warm-blooded mammal, such as a human being.

Tyrosine kinases include both receptor tyrosine kinases and intracellular tyrosine kinases.

Receptor tyrosine kinases include, but are not limited to, receptors for the following growth factors: VEGF, FGF, epidermal growth factor, insulin-like growth factor, insulin,
5 hepatocyte growth factor and platelet-derived growth factor.

Receptor tyrosine kinases include receptors with intrinsic tyrosine kinase activity and receptors which activate associated tyrosine kinases, for example the insulin receptor.

Intracellular tyrosine kinases include, but are not limited to, src and focal adhesion kinase (FAK).

10 The activity of a tyrosine kinase can be blocked in a number of way including, but not restricted to: inhibiting the tyrosine kinase activity, blocking the binding of a ligand to the receptor for example using an antibody, using a receptor antagonist or altering the conformation of the kinase, for example using a compound which binds to an allosteric site.

The signalling of the tyrosine kinase may be blocked at the level of the tyrosine
15 kinase or may be blocked at a level further down the signalling pathway modulating the activity of a component whose activity is modulated by activation of the tyrosine kinase.

According to a further aspect of the present invention there is provided a method of treatment of a disease state associated with angiogenesis which comprises the administration of an effective amount of a combination of an anti-angiogenic agent, which modulates the
20 activity of a tyrosine kinase having vascular effects, and an anti-hypertensive agent to a warm-blooded animal, such as a human being.

According to a further feature of the invention there is provided the use of a combination of an anti-angiogenic agent, which modulates the activity of a tyrosine kinase having vascular effects, and an anti-hypertensive agent for use in the manufacture of a
25 medicament for the treatment of a disease state associated with angiogenesis in a warm-blooded mammal, such as a human being.

According to a further feature of the invention there is provided a pharmaceutical composition comprising a combination of an anti-angiogenic agent, which modulates the activity of a tyrosine kinase having vascular effects, and an anti-hypertensive agent for the
30 treatment of a disease state associated with angiogenesis in a warm-blooded mammal, such as a human being.

Tyrosine kinases which have vascular effects include, but are not limited to, receptors for the following growth factors: VEGF, FGF, epidermal growth factor, insulin-like growth factor, insulin, hepatocyte growth factor and platelet-derived growth factor.

According to a further aspect of the present invention there is provided a method of
5 treatment of a disease state associated with angiogenesis which comprises the administration of an effective amount of a combination of a tyrosine kinase inhibitor, which modulates the level of nitric oxide, and an anti-hypertensive agent to a warm-blooded animal, such as a human being.

According to a further feature of the invention there is provided the use of a
10 combination of a tyrosine kinase inhibitor, which modulates the level of nitric oxide, and an anti-hypertensive agent for use in the manufacture of a medicament for the treatment of a disease state associated with angiogenesis in a warm-blooded mammal, such as a human being.

According to a further feature of the invention there is provided a pharmaceutical
15 composition comprising a combination of a tyrosine kinase inhibitor, which modulates the level of nitric oxide, and an anti-hypertensive agent for the treatment of a disease state associated with angiogenesis in a warm-blooded mammal, such as a human being.

Tyrosine kinases which modulate the level of nitric oxide include the VEGF receptor and the FGF receptor.

20 Combinations of the invention may be administered sequentially or may be administered simultaneously. When administered sequentially either the anti-angiogenic agent or the anti-hypertensive agent may be administered first.

An anti-hypertensive is any agent which lowers blood pressure. There are many different categories of anti-hypertensive agents including calcium channel blockers,
25 angiotensin converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor antagonists (A-II antagonists), diuretics, beta-adrenergic receptor blockers (β -blockers), vasodilators and alpha-adrenergic receptor blockers (α -blockers). Any anti-hypertensive agent may be used in accordance with this invention and examples from each class are given hereinafter.

30 Calcium channel blockers which are within the scope of this invention include, but are not limited to: amlodipine (U.S. Patent No. 4,572,909); bepridil (U.S. Patent No.

3,962,238 or U.S. Reissue No. 30,577); clentiazem (U.S. Patent No. 4,567,175); diltiazem (U.S. Patent No. 3,562,257); fendiline (U.S. Patent No. 3,262,977); gallopamil (U.S. Patent No. 3,261,859); mibefradil (U.S. Patent No. 4,808,605); prenylamine (U.S. Patent No. 3,152,173); semotiadil (U.S. Patent No. 4,786,635); terodiline (U.S. Patent No. 3,371,014);
5 verapamil (U.S. Patent No. 3,261,859); aranidipine (U.S. Patent No. 4,446,325); barnidipine (U.S. Patent No. 4,220,649); benidipine (European Patent Application Publication No. 106,275); cilnidipine (U.S. Patent No. 4,672,068); efonidipine (U.S. Patent No. 4,885,284); elgodipine (U.S. Patent No. 4,952,592); felodipine (U.S. Patent No. 4,264,611); isradipine (U.S. Patent No. 4,466,972); lacidipine (U.S. Patent No. 4,801,599); lercanidipine (U.S.
10 Patent No. 4,705,797); manidipine (U.S. Patent No. 4,892,875); nicardipine (U.S. Patent No. 3,985,758); nifedipine (U.S. Patent No. 3,485,847); nilvadipine (U.S. Patent No. 4,338,322); nimodipine (U.S. Patent No. 3,799,934); nisoldipine (U.S. Patent No. 4,154,839); nitrendipine (U.S. Patent No. 3,799,934); cinnarizine (U.S. Patent No. 2,882,271); flunarizine (U.S. Patent No. 3,773,939); lidoflazine (U.S. Patent No.
15 3,267,104); lomerizine (U.S. Patent No. 4,663,325); bencyclane (Hungarian Patent No. 151,865); etafenone (German Patent No. 1,265,758); and perhexiline (British Patent No. 1,025,578). The disclosures of all such patents and patent applications are incorporated herein by reference.

Angiotensin Converting Enzyme Inhibitors (ACE-Inhibitors) which are within the
20 scope of this invention include, but are not limited to: alacepril (U.S. Patent No. 4,248,883); benazepril (U.S. Patent No. 4,410,520); captopril (U.S. Patents Nos. 4,046,889 and 4,105,776); ceronapril (U.S. Patent No. 4,452,790); delapril (U.S. Patent No. 4,385,051); enalapril (U.S. Patent No. 4,374,829); fosinopril (U.S. Patent No. 4,337,201); imidapril (U.S. Patent No. 4,508,727); lisinopril (U.S. Patent No. 4,555,502); moveltipril (Belgium
25 Patent No. 893,553); perindopril (U.S. Patent No. 4,508,729); quinapril (U.S. Patent No. 4,344,949); ramipril (U.S. Patent No. 4,587,258); spirapril (U.S. Patent No. 4,470,972); temocapril (U.S. Patent No. 4,699,905); and trandolapril (U.S. Patent No. 4,933,361). The disclosures of all such patents are incorporated herein by reference.

Angiotensin-II receptor antagonists (A-II antagonists) which are within the scope of
30 this invention include, but are not limited to: candesartan (U.S. Patent No. 5,196,444); eprosartan (U.S. Patent No. 5,185,351); irbesartan (U.S. Patent No. 5,270,317); losartan

(U.S. Patent No. 5,138,069); and valsartan (U.S. Patent No. 5,399,578. The disclosures of all such U.S. patents are incorporated herein by reference.

β -Blockers which are within the scope of this invention include, but are not limited to: acebutolol (U.S. Patent No. 3,857,952); alprenolol (Netherlands Patent Application No. 6,605,692); amosulalol (U.S. Patent No. 4,217,305); arotinolol (U.S. Patent No. 3,932,400); atenolol (U.S. Patents Nos. 3,663,607 and 3,836,671); befunolol (U.S. Patent No. 3,853,923); betaxolol (U.S. Patent No. 4,252,984); bevantolol (U.S. Patent No. 3,857,891); bisoprolol (U.S. Patent No. 4,258,062); bopindolol (U.S. Patent No. 4,340,541); bucumolol (U.S. Patent No. 3,663,570); bufetolol (U.S. Patent No. 3,723,476); bufuralol (U.S. Patent No. 3,929,836); bunitrolol (U.S. Patent No. 3,541,130); bupranolol (U.S. Patent No. 3,309,406); butidine hydrochloride (French Patent No. 1,390,056); butofilolol (U.S. Patent No. 4,302,601); carazolol (German Patent No. 2,240,599); carteolol (U.S. Patent No. 3,910,924); carvedilol (U.S. Patent No. 4,503,067); celiprolol (U.S. Patent No. 4,034,009); cetamolol (U.S. Patent No. 4,059,622); cloranolol (German Patent No. 2,213,044); dilevalol (Clifton et al., Journal of Medicinal Chemistry, 1982, 25, 670); epanolol (U.S. Patent No. 4,167,581); indenolol (U.S. Patent No. 4,045,482); labetalol (U.S. Patent No. 4,012,444); levobunolol (U.S. Patent No. 4,463,176); mepindolol (Seeman et al, Helv. Chim. Acta, 1971, 54, 2411); metipranolol (Czechoslovakian Patent Application No. 128,471); metoprolol (U.S. Patent No. 3,873,600); moprolol (U.S. Patent No. 3,501,769); nadolol (U.S. Patent No. 3,935,267); nadoxolol (U.S. Patent No. 3,819,702); nebivalol (U.S. Patent No. 4,654,362); nipradilol (U.S. Patent No. 4,394,382); oxprenolol (British Patent No. 1,077,603); penbutolol (U.S. Patent No. 3,551,493); pindolol (Swiss Patents Nos. 469,002 and 472,404); practolol (U.S. Patent No. 3,408,387); pronethalol (British Patent No. 909,357); propranolol (U.S. Patents Nos. 3,337,628 and 3,520,919); sotalol (Uloth et al., Journal of Medicinal Chemistry, 1966, 9, 88); sulfinalol (German Patent No. 2,728,641); talinolol (U.S. Patents Nos. 3,935,259 and 4,038,313); tertatolol (U.S. Patent No. 3,960,891); tilisolol (U.S. Patent No. 4,129,565); timolol (U.S. Patent No. 3,655,663); toliprolol (U.S. Patent No. 3,432,545); and xibenolol (U.S. Patent No. 4,018,824. The disclosures of all such patents, patent applications and references are incorporated herein by reference.

α -Blockers which are within the scope of this invention include, but are not limited to: amosulalol (U.S. Patent No. 4,217,305); arotinolol (which may be prepared as described hereinbefore); dapiprazole (U.S. Patent No. 4,252,721); doxazosin (U.S. Patent No. 4,188,390); fenspiride (U.S. Patent No. 3,399,192); indoramin (U.S. Patent No. 3,527,761); 5 labetolol, naftopidil (U.S. Patent No. 3,997,666); nicergoline (U.S. Patent No. 3,228,943); prazosin (U.S. Patent No. 3,511,836); tamsulosin (U.S. Patent No. 4,703,063); tolazoline (U.S. Patent No. 2,161,938); trimazosin (U.S. Patent No. 3,669,968); and yohimbine, which may be isolated from natural sources according to methods well known to those skilled in the art. The disclosures of all such U.S. patents are incorporated herein by reference.

10 The term "vasodilator", where used herein, is meant to include cerebral vasodilators, coronary vasodilators and peripheral vasodilators. Cerebral vasodilators within the scope of this invention include, but are not limited to: bencyclane (which may be prepared as described hereinbefore); cinnarizine (which may be prepared as described hereinbefore); citicoline, which may be isolated from natural sources as disclosed in Kennedy et al., 15 Journal of the American Chemical Society, 1955, 77, 250 or synthesised as disclosed in Kennedy, Journal of Biological Chemistry, 1956, 222, 185; cyclandelate (U.S. Patent No. 3,663,597); ciclonicate (German Patent No. 1,910,481); diisopropylamine dichloroacetate (British Patent No. 862,248); eburnamonine (Hermann et al., Journal of the American Chemical Society, 1979, 101, 1540); fasudil (U.S. Patent No. 4,678,783); fenoxedil (U.S. 20 Patent No. 3,818,021); flunarizine (U.S. Patent No. 3,773,939); ibudilast (U.S. Patent No. 3,850,941); ifenprodil (U.S. Patent No. 3,509,164); lomerizine (U.S. Patent No. 4,663,325); nafronyl (U.S. Patent No. 3,334,096); nicametate (Blicke et al., Journal of the American Chemical Society, 1942, 64, 1722); nicergoline (which may be prepared as described hereinbefore); nimodipine (U.S. Patent No. 3,799,934); papaverine, which may be prepared 25 as reviewed in Goldberg, Chem. Prod. Chem. News, 1954, 17, 371; pentifylline (German Patent No. 860,217); tinofedrine (U.S. Patent No. 3,767,675); vincamine (U.S. Patent No. 3,770,724); vinpocetine (U.S. Patent No. 4,035,750); and viquidil (U.S. Patent No. 2,500,444. The disclosures of all such patents and references are incorporated herein by reference.

30 Coronary vasodilators within the scope of this invention include, but are not limited to: amotriphene (U.S. Patent No. 3,010,965); bendazol (Feitelson, et al., J. Chem. Soc. 1958,

2426); benfurodil hemisuccinate (U.S. Patent No. 3,355,463); benziodarone (U.S. Patent No. 3,012,042); chloracizine (British Patent No. 740,932); chromonar (U.S. Patent No. 3,282,938); clobenfuril (British Patent No. 1,160,925); clonitrate, which may be prepared from propanediol according to methods well known to those skilled in the art, e.g., see
5 *Annalen*, 1870, 155, 165; cloricromen (U.S. Patent No. 4,452,811); dilazep (U.S. Patent No. 3,532,685); dipyridamole (British Patent No. 807,826); droprenilamine (German Patent No. 2,521,113); efloxate (British Patents Nos. 803,372 and 824,547); erythrityl tetranitrate, which may be prepared by nitration of erythritol according to methods well-known to those skilled in the art; etafenone (German Patent No. 1,265,758); fendiline (U.S. Patent No.
10 3,262,977); floredil (German Patent No. 2,020,464); gangliefene (U.S.S.R. Patent No. 115,905); hexestrol bis(β -diethylaminoethyl) ether (Lowe et al., *J. Chem. Soc.* 1951, 3286); hexobendine (U.S. Patent No. 3,267,103); itramin tosylate (Swedish Patent No. 168,308); khellin (Baxter et al., *Journal of the Chemical Society*, 1949, S 30); lidoflazine (U.S. Patent No. 3,267,104); mannitol hexanitrate, which may be prepared by the nitration of mannitol
15 according to methods well-known to those skilled in the art; medibazine (U.S. Patent No. 3,119,826); nitroglycerin; pentaerythritol tetranitrate, which may be prepared by the nitration of pentaerythritol according to methods well-known to those skilled in the art; pentrinitrol (German Patent No. 638,422-3); perhexiline (which may be prepared as described hereinbefore); pimefylline (U.S. Patent No. 3,350,400); prenylamine (U.S. Patent
20 No. 3,152,173); propatyl nitrate (French Patent No. 1,103,113); trapidil (East German Patent No. 55,956); tricromyl (U.S. Patent No. 2,769,015); trimetazidine (U.S. Patent No. 3,262,852); trolnitrate phosphate, which may be prepared by nitration of triethanolamine followed by precipitation with phosphoric acid according to methods well-known to those skilled in the art; visnadine (U.S. Patents Nos. 2,816,118 and 2,980,699). The disclosures of
25 all such patents and references are incorporated herein by reference.

Peripheral vasodilators within the scope of this invention include, but are not limited to: aluminium nicotinate (U.S. Patent No. 2,970,082); bamethan (Corrigan et al., *Journal of the American Chemical Society*, 1945, 67, 1894); bencyclane (which may be prepared as described herein before); betahistine (Walter et al, *Journal of the American Chemical*
30 *Society*, 1941, 63, 2771); bradykinin (Hamburg et al., *Arch. Biochem. Biophys.*, 1958, 76, 252); brovincamine (U.S. Patent No. 4,146,643); bufeniode (U.S. Patent No. 3,542,870);

buflomedil (U.S. Patent No. 3,895,030); butalamine (U.S. Patent No. 3,338,899); cetiedil (French Patent No. 1,460,571); ciclonicate (German Patent No. 1,910,481); cinepazide (Belguim Patent No. 730,345); cinnarizine (which may be prepared as described herein before); cyclandelate (which may be prepared as described hereinbefore); diisopropylamine
5 dichloroacetate (which may be prepared as described hereinbefore); eledoisin (British Patent No. 984,810); fenoxedil (which may be prepared as described hereinbefore); flunarizine (which may be prepared as described hereinbefore); hepronicate (U.S. Patent No. 3,384,642); ifenprodil (which may be prepared as described hereinbefore); iloprost (U.S. Patent No. 4,692,464); inositol niacinate (Badgett et al., Journal of the American Chemical
10 Society, 1947, 69, 2907); isoxsuprine (U.S. Patent No. 3,056,836); kallidin (Nicolaidis et al., Biochem. Biophys. Res. Commun., 1961, 6, 210); kallikrein (German Patent No. 1,102,973); moxislyte (German Patent No. 905,738); nafronyl (which may be prepared as described herein before); nicametate (which may be prepared as described herein before); nicergoline (which may be prepared as described hereinbefore); nicofuranose (Swiss Patent
15 No. 366,523); nylidrin (U.S. Patents Nos. 2,661,372 and 2,661,373); pentifylline (which may be prepared as described hereinbefore); pentoxifylline, which may be prepared as disclosed U.S. Patent No. 3,422,107); piribedil (U.S. Patent No. 3,299,067); prostaglandin E₁, which may be prepared by any of the methods referenced in the Merck Index, Twelfth Edition, Budaveri, Ed, New Jersey 1996, page 1353); suloctidil (German Patent No.
20 2,334,404); tolazoline (U.S. Patent No. 2,161,938); and xanthinol niacinate (German Patent No. 1,102,750 or Korbonits et al, Acta. Pharm. Hung., 1968, 38, 98. The disclosures of all such patents and references are incorporated herein by reference.

The term "diuretic", within the scope of this invention, includes but is not limited to diuretic benzothiadiazine derivatives, diuretic organomercurials, diuretic purines, diuretic
25 steroids, diuretic sulfonamide derivatives, diuretic uracils and other diuretics such as amanozine (Austrian Patent No. 168,063); amiloride (Belguim Patent No. 639,386); arbutin (Tschitschibabin et al., Annalen, 1930, 479, 303); chlorazaniil (Austrian Patent No. 168,063); ethacrynic acid (U.S. Patent No. 3,255,241); etozolin (U.S. Patent No. 3,072,653); hydracarbazine (British Patent No. 856,409); isosorbide (U.S. Patent No. 3,160,641);
30 mannitol; metochalcone (Freudenberg et al., Ber., 1957, 90, 957); muzolimine (U.S. Patent No. 4,018,890); perhexiline (which may be prepared as described hereinbefore); ticrynafen

(U.S. Patent No. 3,758,506); triamterene (U.S. Patent No. 3,081,230); and urea. The disclosures of all such patents and references are incorporated herein by reference.

Diuretic benzothiadiazine derivatives within the scope of this invention include, but are not limited to: althiazide (British Patent No. 902,658); bendroflumethiazide (U.S. Patent
5 No. 3,392,168); benzthiazide (U.S. Patent No. 3,440,244); benzylhydrochlorothiazide (U.S. Patent No. 3,108,097); buthiazide (British Patents Nos. 861,367 and 885,078); chlorothiazide (U.S. Patents Nos. 2,809,194 and 2,937,169); chlorthalidone (U.S. Patent No. 3,055,904); cyclopenthiazide (Belguim Patent No. 587,225); cyclothiazide (Whitehead et al., Journal of Organic Chemistry, 1961, 26, 2814); epithiazide (U.S. Patent No. 3,009,911);
10 ethiazide (British Patent No. 861,367); fenquizone (U.S. Patent No. 3,870,720); indapamide (U.S. Patent No. 3,565,911); hydrochlorothiazide (U.S. Patent No. 3,164,588); hydroflumethiazide (U.S. Patent No. 3,254,076); methyclothiazide (Close et al., Journal of the American Chemical Society, 1960, 82, 1132); meticrane (French Patents Nos. M2790 and 1,365,504); metolazone (U.S. Patent No. 3,360,518); paraflutizide (Belguim Patent No.
15 620,829); polythiazide (U.S. Patent No. 3,009,911); quinethazone (U.S. Patent No. 2,976,289); teclothiazide (Close et al., Journal of the American Chemical Society, 1960, 82, 1132); and trichlormethiazide (deStevens et al., *Experientia*, 1960, 16, 113). The disclosures of all such patents and references are incorporated herein by reference.

Diuretic sulfonamide derivatives within the scope of this invention include, but are
20 not limited to: acetazolamide (U.S. Patent No. 2,554,816); ambuside (U.S. Patent No. 3,188,329); azosemide (U.S. Patent No. 3,665,002); bumetanide (U.S. Patent No. 3,806,534); butazolamide (British Patent No. 769,757); chloraminophenamide (U.S. Patents Nos. 2,809,194, 2,965,655 and 2,965,656); clofenamide (Olivier, *Rec. Trav. Chim.*, 1918, 37, 307); clopamide (U.S. Patent No. 3,459,756); clorexolone (U.S. Patent No. 3,183,243);
25 disulfamide (British Patent No. 851,287); ethozolamide (British Patent No. 795,174); furosemide (U.S. Patent No. 3,058,882); mefruside (U.S. Patent No. 3,356,692); methazolamide (U.S. Patent No. 2,783,241); piretanide (U.S. Patent No. 4,010,273); torsemide (U.S. Patent No. 4,018,929); tripamide (Japanese Patent No. 73 05,585); and xipamide (U.S. Patent No. 3,567,777. The disclosures of all such patents and references are
30 incorporated herein by reference.

Further, the anti-hypertensive agents which may be used in accordance with this invention and the pharmaceutically acceptable salts thereof may occur as prodrugs, hydrates or solvates. Said hydrates and solvates are also within the scope of the present invention.

Preferred anti-hypertensive agents of the invention include, calcium channel
5 blockers, A-II antagonists, ACE inhibitors and β -blockers.

More preferred anti-hypertensive agents of the invention include ACE inhibitors, particularly lisinopril and captopril.

The anti-hypertensives described herein are generally commercially available, or they may be made by standard techniques including those described in the references given
10 hereinbefore.

An anti-angiogenic agent is any agent which inhibits the growth and maintenance of new blood vessels. There are many different categories of anti-angiogenic agents which include, but not limited to: agents which inhibit the action of growth factors; anti-invasive agents; and vascular targeting agents.

15 Agents which inhibit the action of growth factors include, but not limited to:

- (i) receptor antagonists, for example, an anti-VEGF receptor antibody (Genentech, Canadian Patent Application No. 2213833)
- (ii) protein kinase C inhibitors;
- (iii) tyrosine kinase inhibitors, for example inhibitors of VEGF receptor tyrosine kinase,
20 such as SU 5416, (Sugen, International Patent Application Publication No. WO 96/40116); and
- (iv) modulators of the signalling of the receptors Tie-1 and/or Tie 2;
- (v) inhibitors of protein expression, for example, inhibitors of VEGF expression, such as RPI 4610 (Ribozyme, U.S. Patent No. 4987071).

25 Anti-invasion agents include matrix metalloproteinase inhibitors and urokinase plasminogen activator receptor antagonist and urokinase plasminogen activator inhibitors. Matrix metalloproteinase inhibitors include: prinomastat (Agouron, U.S. Patent No. 5753653); ilomastat (Glycomed, International Patent Application Publication No. WO 92/9556); marimastat (British Biotechnology, International Patent Application Publication
30 No. WO 94/2447; and batimastat (British Biotechnology, International Patent Application Publication No. WO 90/5719). Urokinase plasminogen activator receptor antagonists

include: compounds disclosed in International Patent Application Publication No.

WO96/40747 and compounds disclosed in International Patent Application Publication No.

WO 2000001802. Urokinase plasminogen activator inhibitors include: compounds disclosed in International Patent Application Publication No. WO 2000005245.

- 5 Vascular targeting agents include: Combretastatin A4 (Bristol Myers Squibb, US Patent No. 4996237); and vascular damaging agents described in International Patent Applications Publication Nos. WO 99/02166 and WO 00/40529 the entire disclosure of which is incorporated herein by reference. A particularly preferred vascular damaging agent is

- 10 N-acetylcolchicinol-O-phosphate (Example 1 of WO 99/02166).

Other anti-angiogenic agents include: AE 941 (Neovastat), isolated from shark cartilage (Aeterna, U.S. Patent Nos. 5618925, 5985839, and 6025334); thalidomide (Celgene, U.S. Patent No. 5463063); and Vitaxin (LM609, an anti-integrin antibody Cell 1994 79 1157-1164).

- 15 Preferred anti-angiogenic agents are agents which inhibit the action of growth factors, particularly tyrosine kinase inhibitors. Most preferred are VEGF receptor tyrosine kinase inhibitors.

Preferred VEGF receptor tyrosine kinase inhibitors include those described in International Patent Applications Publication Nos. WO 97/22596, WO 97/30035,

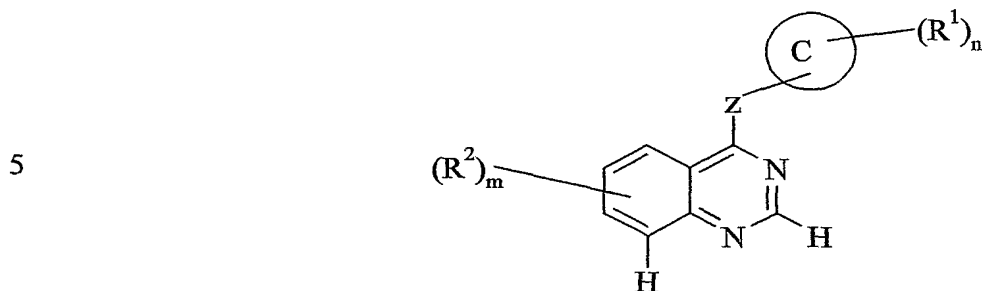
- 20 WO 97/32856, WO 97/34876, WO 97/42187, WO 98/13354, WO 98/13350, WO 99/10349, WO 00/21955 and WO 00/47212, the entire disclosure of each of said applications is incorporated herein by reference.

Preferred VEGF receptor tyrosine kinase inhibitors are described in WO 00/47212 and are of the formula I:

25

30

- 17 -



formula I

10

wherein:

ring C is an 8, 9, 10, 12 or 13-membered bicyclic or tricyclic moiety which moiety may be saturated or unsaturated, which may be aromatic or non-aromatic, and which optionally may contain 1-3 heteroatoms selected independently from O, N and S;

15 Z is -O-, -NH-, -S-, -CH₂- or a direct bond;

n is an integer from 0 to 5;

m is an integer from 0 to 3;

R² represents hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, C₁₋₃alkyl,

C₁₋₃alkoxy, C₁₋₃alkylsulphanyl, -NR³R⁴ (wherein R³ and R⁴, which may be the same or

20 different, each represents hydrogen or C₁₋₃alkyl), or R⁵X¹- (wherein X¹ represents a direct bond, -O-, -CH₂-, -OC(O)-, -C(O)-, -S-, -SO-, -SO₂-, -NR⁶C(O)-, -C(O)NR⁷-, -SO₂NR⁸-, -NR⁹SO₂- or -NR¹⁰- (wherein R⁶, R⁷, R⁸, R⁹ and R¹⁰ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl), and R⁵ is selected from one of the following twenty-two groups:

25 1) hydrogen, oxiranylC₁₋₄alkyl or C₁₋₅alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, chloro, bromo and amino;

2) C₁₋₅alkylX²C(O)R¹¹ (wherein X² represents -O- or -NR¹²- (in which R¹² represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹¹ represents C₁₋₃alkyl, -NR¹³R¹⁴ or -OR¹⁵

30 (wherein R¹³, R¹⁴ and R¹⁵ which may be the same or different each represents hydrogen, C₁₋₅alkyl or C₁₋₃alkoxyC₂₋₃alkyl));

3) C₁₋₅alkylX³R¹⁶ (wherein X³ represents -O-, -S-, -SO-, -SO₂-, -OC(O)-, -NR¹⁷C(O)-, -C(O)NR¹⁸-, -SO₂NR¹⁹-, -NR²⁰SO₂- or -NR²¹- (wherein R¹⁷, R¹⁸, R¹⁹, R²⁰ and R²¹ each

- independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹⁶ represents hydrogen, C₁₋₃alkyl, cyclopentyl, cyclohexyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C₁₋₃alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C₁₋₄alkoxy and which
- 5 cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₄cyanoalkyl, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl, C₁₋₄alkylsulphonylC₁₋₄alkyl, C₁₋₄alkoxycarbonyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, C₁₋₄alkylaminoC₁₋₄alkyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl, C₁₋₄alkylaminoC₁₋₄alkoxy, di(C₁₋₄alkyl)aminoC₁₋₄alkoxy and a group $-(O)_f(C_{1-4}alkyl)_g ringD$ (wherein f is 0 or
- 10 1, g is 0 or 1 and ring D is a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C₁₋₄alkyl));
- 4) C₁₋₅alkylX⁴C₁₋₅alkylX⁵R²² (wherein X⁴ and X⁵ which may be the same or different are each -O-, -S-, -SO-, -SO₂-, -NR²³C(O)-, -C(O)NR²⁴-, -SO₂NR²⁵-, -NR²⁶SO₂- or -NR²⁷-
- 15 (wherein R²³, R²⁴, R²⁵, R²⁶ and R²⁷ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²² represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl);
- 5) R²⁸ (wherein R²⁸ is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₄cyanoalkyl, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl,
- 20 C₁₋₄alkylsulphonylC₁₋₄alkyl, C₁₋₄alkoxycarbonyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, C₁₋₄alkylaminoC₁₋₄alkyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl, C₁₋₄alkylaminoC₁₋₄alkoxy, di(C₁₋₄alkyl)aminoC₁₋₄alkoxy and a group $-(O)_f(C_{1-4}alkyl)_g ringD$ (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated heterocyclic group with 1-2
- 25 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C₁₋₄alkyl));
- 6) C₁₋₅alkylR²⁸ (wherein R²⁸ is as defined herein);
- 7) C₂₋₅alkenylR²⁸ (wherein R²⁸ is as defined herein);
- 8) C₂₋₅alkynylR²⁸ (wherein R²⁸ is as defined herein);
- 30 9) R²⁹ (wherein R²⁹ represents a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-3 heteroatoms selected

- from O, N and S, which pyridone, phenyl or aromatic heterocyclic group may carry up to 5 substituents selected from hydroxy, halogeno, amino, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy, carboxy, trifluoromethyl, cyano, -C(O)NR³⁰R³¹, -NR³²C(O)R³³ (wherein R³⁰, R³¹, R³² and R³³, which may be the same or different, each represents hydrogen, C₁₋₄alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and a group -(O-)(C₁₋₄alkyl)_fringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C₁₋₄alkyl));
- 10) C₁₋₅alkylR²⁹ (wherein R²⁹ is as defined herein);
- 10 11) C₂₋₅alkenylR²⁹ (wherein R²⁹ is as defined herein);
- 12) C₂₋₅alkynylR²⁹ (wherein R²⁹ is as defined herein);
- 13) C₁₋₅alkylX⁶R²⁹ (wherein X⁶ represents -O-, -S-, -SO-, -SO₂-, -NR³⁴C(O)-, -C(O)NR³⁵-, -SO₂NR³⁶-, -NR³⁷SO₂- or -NR³⁸- (wherein R³⁴, R³⁵, R³⁶, R³⁷ and R³⁸ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁹ is as defined herein);
- 15 14) C₂₋₅alkenylX⁷R²⁹ (wherein X⁷ represents -O-, -S-, -SO-, -SO₂-, -NR³⁹C(O)-, -C(O)NR⁴⁰-, -SO₂NR⁴¹-, -NR⁴²SO₂- or -NR⁴³- (wherein R³⁹, R⁴⁰, R⁴¹, R⁴² and R⁴³ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁹ is as defined herein);
- 15) C₂₋₅alkynylX⁸R²⁹ (wherein X⁸ represents -O-, -S-, -SO-, -SO₂-, -NR⁴⁴C(O)-, -C(O)NR⁴⁵-, -SO₂NR⁴⁶-, -NR⁴⁷SO₂- or -NR⁴⁸- (wherein R⁴⁴, R⁴⁵, R⁴⁶, R⁴⁷ and R⁴⁸ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁹ is as defined herein);
- 20 16) C₁₋₄alkylX⁹C₁₋₄alkylR²⁹ (wherein X⁹ represents -O-, -S-, -SO-, -SO₂-, -NR⁴⁹C(O)-, -C(O)NR⁵⁰-, -SO₂NR⁵¹-, -NR⁵²SO₂- or -NR⁵³- (wherein R⁴⁹, R⁵⁰, R⁵¹, R⁵² and R⁵³ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁹ is as defined herein);
- 25 17) C₁₋₄alkylX⁹C₁₋₄alkylR²⁸ (wherein X⁹ and R²⁸ are as defined herein);
- 18) C₂₋₅alkenyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C₁₋₄alkylamino, N,N-di(C₁₋₄alkyl)amino, aminosulphonyl, N-C₁₋₄alkylaminosulphonyl and N,N-di(C₁₋₄alkyl)aminosulphonyl;
- 19) C₂₋₅alkynyl which may be unsubstituted or which may be substituted with one or more
- 30 groups selected from hydroxy, fluoro, amino, C₁₋₄alkylamino, N,N-di(C₁₋₄alkyl)amino, aminosulphonyl, N-C₁₋₄alkylaminosulphonyl and N,N-di(C₁₋₄alkyl)aminosulphonyl;

- 20) $C_{2-5}alkenylX^9C_{1-4}alkylR^{28}$ (wherein X^9 and R^{28} are as defined herein);
- 21) $C_{2-5}alkynylX^9C_{1-4}alkylR^{28}$ (wherein X^9 and R^{28} are as defined herein); and
- 22) $C_{1-4}alkylR^{54}(C_{1-4}alkyl)_q(X^9)_rR^{55}$ (wherein X^9 is as defined herein, q is 0 or 1, r is 0 or 1, and R^{54} and R^{55} are each independently selected from hydrogen, $C_{1-3}alkyl$, cyclopentyl, cyclohexyl and a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which $C_{1-3}alkyl$ group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and $C_{1-4}alkoxy$ and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, $C_{1-4}cyanoalkyl$, $C_{1-4}alkyl$, $C_{1-4}hydroxyalkyl$, $C_{1-4}alkoxy$, $C_{1-4}alkoxyC_{1-4}alkyl$, $C_{1-4}alkylsulphonylC_{1-4}alkyl$, $C_{1-4}alkoxycarbonyl$, $C_{1-4}aminoalkyl$, $C_{1-4}alkylamino$, $di(C_{1-4}alkyl)amino$, $C_{1-4}alkylaminoC_{1-4}alkyl$, $di(C_{1-4}alkyl)aminoC_{1-4}alkyl$, $C_{1-4}alkylaminoC_{1-4}alkoxy$, $di(C_{1-4}alkyl)aminoC_{1-4}alkoxy$ and a group $-(O-)_f(C_{1-4}alkyl)_gringD$ (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from $C_{1-4}alkyl$),
- 15 with the proviso that R^{54} cannot be hydrogen);
- and additionally wherein any $C_{1-5}alkyl$, $C_{2-5}alkenyl$ or $C_{2-5}alkynyl$ group in R^5X^1 may bear one or more substituents selected from hydroxy, halogeno and amino);
- R^1 represents hydrogen, oxo, halogeno, hydroxy, $C_{1-4}alkoxy$, $C_{1-4}alkyl$, $C_{1-4}alkoxymethyl$, $C_{1-4}alkanoyl$, $C_{1-4}haloalkyl$, cyano, amino, $C_{2-5}alkenyl$, $C_{2-5}alkynyl$, $C_{1-3}alkanoyloxy$, nitro, $C_{1-4}alkanoylamino$, $C_{1-4}alkoxycarbonyl$, $C_{1-4}alkylsulphanyl$, $C_{1-4}alkylsulphinyl$, $C_{1-4}alkylsulphonyl$, carbamoyl, \underline{N} - $C_{1-4}alkylcarbamoyl$, $\underline{N,N}$ - $di(C_{1-4}alkyl)carbamoyl$, aminosulphonyl, \underline{N} - $C_{1-4}alkylaminosulphonyl$, $\underline{N,N}$ - $di(C_{1-4}alkyl)aminosulphonyl$, \underline{N} -($C_{1-4}alkylsulphonyl$)amino, \underline{N} -($C_{1-4}alkylsulphonyl$)- \underline{N} -($C_{1-4}alkyl$)amino, $\underline{N,N}$ - $di(C_{1-4}alkylsulphonyl)amino$, a $C_{3-7}alkylene$ chain joined to two ring C carbon atoms, $C_{1-4}alkanoylaminoC_{1-4}alkyl$, carboxy or a group $R^{56}X^{10}$ (wherein X^{10} represents a direct bond, -O-, $-CH_2-$, $-OC(O)-$, $-C(O)-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^{57}C(O)-$, $-C(O)NR^{58}-$, $-SO_2NR^{59}-$, $-NR^{60}SO_2-$ or $-NR^{61}-$, (wherein R^{57} , R^{58} , R^{59} , R^{60} and R^{61} each independently represents hydrogen, $C_{1-3}alkyl$ or $C_{1-3}alkoxyC_{2-3}alkyl$), and R^{56} is selected from one of the following twenty-two groups:

- 1) hydrogen, oxiranylC₁₋₄alkyl or C₁₋₅alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, chloro, bromo and amino;
- 2) C₁₋₅alkylX¹¹C(O)R⁶² (wherein X¹¹ represents -O- or -NR⁶³- (in which R⁶³ represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R⁶² represents C₁₋₃alkyl, -NR⁶⁴R⁶⁵ or -OR⁶⁶ (wherein R⁶⁴, R⁶⁵ and R⁶⁶ which may be the same or different each represents hydrogen, C₁₋₅alkyl or C₁₋₃alkoxyC₂₋₃alkyl));
- 3) C₁₋₅alkylX¹²R⁶⁷ (wherein X¹² represents -O-, -S-, -SO-, -SO₂-, -OC(O)-, -NR⁶⁸C(O)-, -C(O)NR⁶⁹-, -SO₂NR⁷⁰-, -NR⁷¹SO₂- or -NR⁷²- (wherein R⁶⁸, R⁶⁹, R⁷⁰, R⁷¹ and R⁷² each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R⁶⁷ represents hydrogen, C₁₋₃alkyl, cyclopentyl, cyclohexyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C₁₋₃alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C₁₋₄alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₄cyanoalkyl, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl, C₁₋₄alkylsulphonylC₁₋₄alkyl, C₁₋₄alkoxycarbonyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, C₁₋₄alkylaminoC₁₋₄alkyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl, C₁₋₄alkylaminoC₁₋₄alkoxy, di(C₁₋₄alkyl)aminoC₁₋₄alkoxy and a group -(O)_f(C₁₋₄alkyl)_gringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C₁₋₄alkyl));
- 4) C₁₋₅alkylX¹³C₁₋₅alkylX¹⁴R⁷³ (wherein X¹³ and X¹⁴ which may be the same or different are each -O-, -S-, -SO-, -SO₂-, -NR⁷⁴C(O)-, -C(O)NR⁷⁵-, -SO₂NR⁷⁶-, -NR⁷⁷SO₂- or -NR⁷⁸- (wherein R⁷⁴, R⁷⁵, R⁷⁶, R⁷⁷ and R⁷⁸ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R⁷³ represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl);
- 5) R⁷⁹ (wherein R⁷⁹ is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₄cyanoalkyl, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl, C₁₋₄alkylsulphonylC₁₋₄alkyl, C₁₋₄alkoxycarbonyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, C₁₋₄alkylaminoC₁₋₄alkyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl, C₁₋₄alkylaminoC₁₋₄alkoxy, di(C₁₋₄alkyl)aminoC₁₋₄alkoxy and a group -(O)_f(C₁₋₄alkyl)_gringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C₁₋₄alkyl));

- alkoxy, di(C₁₋₄alkyl)aminoC₁₋₄alkoxy and a group $-(O)_f(C_{1-4}alkyl)_g ringD$ (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C₁₋₄alkyl));
- 5 6) C₁₋₅alkylR⁷⁹ (wherein R⁷⁹ is as defined herein);
 - 7) C₂₋₅alkenylR⁷⁹ (wherein R⁷⁹ is as defined herein);
 - 8) C₂₋₅alkynylR⁷⁹ (wherein R⁷⁹ is as defined herein);
 - 9) R⁸⁰ (wherein R⁸⁰ represents a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-3 heteroatoms selected
 - 10 from O, N and S, which pyridone, phenyl or aromatic heterocyclic group may carry up to 5 substituents selected from hydroxy, halogeno, amino, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy, carboxy, trifluoromethyl, cyano, -C(O)NR⁸¹R⁸², -NR⁸³C(O)R⁸⁴ (wherein R⁸¹, R⁸², R⁸³ and R⁸⁴, which may be the same or different, each represents hydrogen, C₁₋₄alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and a group $-(O)_f(C_{1-4}alkyl)_g ringD$ (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C₁₋₄alkyl));
 - 15 10) C₁₋₅alkylR⁸⁰ (wherein R⁸⁰ is as defined herein);
 - 11) C₂₋₅alkenylR⁸⁰ (wherein R⁸⁰ is as defined herein);
 - 20 12) C₂₋₅alkynylR⁸⁰ (wherein R⁸⁰ is as defined herein);
 - 13) C₁₋₅alkylX¹⁵R⁸⁰ (wherein X¹⁵ represents -O-, -S-, -SO-, -SO₂-, -NR⁸⁵C(O)-, -C(O)NR⁸⁶-, -SO₂NR⁸⁷-, -NR⁸⁸SO₂- or -NR⁸⁹- (wherein R⁸⁵, R⁸⁶, R⁸⁷, R⁸⁸ and R⁸⁹ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R⁸⁰ is as defined herein);
 - 14) C₂₋₅alkenylX¹⁶R⁸⁰ (wherein X¹⁶ represents -O-, -S-, -SO-, -SO₂-, -NR⁹⁰C(O)-, -C(O)NR⁹¹-, -SO₂NR⁹²-, -NR⁹³SO₂- or -NR⁹⁴- (wherein R⁹⁰, R⁹¹, R⁹², R⁹³ and R⁹⁴ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R⁸⁰ is as defined
 - 25 herein);
 - 15) C₂₋₅alkynylX¹⁷R⁸⁰ (wherein X¹⁷ represents -O-, -S-, -SO-, -SO₂-, -NR⁹⁵C(O)-, -C(O)NR⁹⁶-, -SO₂NR⁹⁷-, -NR⁹⁸SO₂- or -NR⁹⁹- (wherein R⁹⁵, R⁹⁶, R⁹⁷, R⁹⁸ and R⁹⁹ each
 - 30 independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R⁸⁰ is as defined herein);

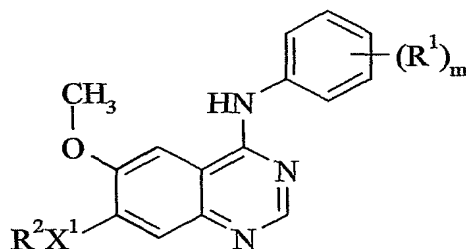
- 16) $C_{1-4}alkylIX^{18}C_{1-4}alkylR^{80}$ (wherein X^{18} represents -O-, -S-, -SO-, -SO₂-, -NR¹⁰⁰C(O)-, -C(O)NR¹⁰¹-, -SO₂NR¹⁰²-, -NR¹⁰³SO₂- or -NR¹⁰⁴- (wherein R¹⁰⁰, R¹⁰¹, R¹⁰², R¹⁰³ and R¹⁰⁴ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R⁸⁰ is as defined herein);
- 5 17) $C_{1-4}alkylIX^{18}C_{1-4}alkylR^{79}$ (wherein X^{18} and R⁷⁹ are as defined herein);
- 18) C₂₋₅alkenyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C₁₋₄alkylamino, N,N-di(C₁₋₄alkyl)amino, aminosulphonyl, N-C₁₋₄alkylaminosulphonyl and N,N-di(C₁₋₄alkyl)aminosulphonyl;
- 19) C₂₋₅alkynyl which may be unsubstituted or which may be substituted with one or more
- 10 groups selected from hydroxy, fluoro, amino, C₁₋₄alkylamino, N,N-di(C₁₋₄alkyl)amino, aminosulphonyl, N-C₁₋₄alkylaminosulphonyl and N,N-di(C₁₋₄alkyl)aminosulphonyl;
- 20) C₂₋₅alkenylX¹⁸C₁₋₄alkylR⁷⁹ (wherein X^{18} and R⁷⁹ are as defined herein);
- 21) C₂₋₅alkynylX¹⁸C₁₋₄alkylR⁷⁹ (wherein X^{18} and R⁷⁹ are as defined herein); and
- 22) $C_{1-4}alkylR^{105}(C_{1-4}alkyl)_x(X^{18})_yR^{106}$ (wherein X^{18} is as defined herein, x is 0 or 1, y is 0 or
- 15 1, and R¹⁰⁵ and R¹⁰⁶ are each independently selected from hydrogen, C₁₋₃alkyl, cyclopentyl, cyclohexyl and a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C₁₋₃alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C₁₋₄alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₄cyanoalkyl, C₁₋₄alkyl, C₁₋
- 20 ₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl, C₁₋₄alkylsulphonylC₁₋₄alkyl, C₁₋
₄alkoxycarbonyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, C₁₋₄alkylaminoC₁₋
₄alkyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl, C₁₋₄alkylaminoC₁₋₄alkoxy, di(C₁₋₄alkyl)aminoC₁₋₄alkoxy
 and a group -(O-)_f(C₁₋₄alkyl)_gringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-
 membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from
- 25 O, S and N, which cyclic group may bear one or more substituents selected from C₁₋₄alkyl) with the proviso that R¹⁰⁵ cannot be hydrogen);
- and additionally wherein any C₁₋₅alkyl, C₂₋₅alkenyl or C₂₋₅alkynyl group in R⁵⁶X¹⁰- may bear one or more substituents selected from hydroxy, halogeno and amino);
- or a pharmaceutically acceptable salt, solvate or pro-drug thereof.
- 30 Preferred compounds of formula I include:
- 6-methoxy-4-(2-methylindol-5-yloxy)-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline,

- 4-(4-fluoroindol-5-yloxy)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline,
 4-(4-fluoroindol-5-yloxy)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline,
 4-(6-fluoroindol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline,
 4-(4-fluoroindol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline,
 5 4-(4-fluoroindol-5-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,
 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline,
 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,
 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline,
 10 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline,
 4-(4-fluoroindol-5-yloxy)-6-methoxy-7-(2-(1-methylpiperidin-4-yl)ethoxy)quinazoline,
 (2*R*)-7-(2-hydroxy-3-(pyrrolidin-1-yl)propoxy)-4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxyquinazoline, and
 15 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(2-(1-methylpiperidin-4-yl)ethoxy)quinazoline,
 and salts thereof especially hydrochloride salts thereof.

In another aspect of the present invention preferred compounds of formula 1 include:

- 20 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline;
 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline;
 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline;
 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline;
 25 (2*R*)-7-(2-hydroxy-3-(pyrrolidin-1-yl)propoxy)-4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxyquinazoline; and
 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(2-(1-methylpiperidin-4-yl)ethoxy)quinazoline.

- 30 A further preferred VEGF receptor tyrosine kinase inhibitor is a compound of the formula II:



formula (II)

[wherein:

5 m is an integer from 1 to 3;

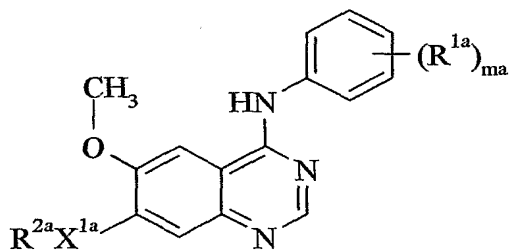
R¹ represents halogeno or C₁₋₃alkyl;

X¹ represents -O-;

R² is selected from one of the following three groups:

- 1) C₁₋₅alkylR^{3a} (wherein R^{3a} is piperidin-4-yl which may bear one or two substituents
 - 10 selected from hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl and C₁₋₄alkoxy;
 - 2) C₂₋₅alkenylR^{3a} (wherein R^{3a} is as defined hereinbefore);
 - 3) C₂₋₅alkynylR^{3a} (wherein R^{3a} is as defined hereinbefore);
- and wherein any alkyl, alkenyl or alkynyl group may bear one or more substituents selected from hydroxy, halogeno and amino;
- 15 or a pharmaceutically acceptable salt, solvate or pro-drug thereof.

A more preferred VEGF receptor tyrosine kinase inhibitor is a compound of the formula III:



formula (III)

20 [wherein:

ma is an integer from 1 to 3;

R^{1a} represents halogeno or C₁₋₃alkyl;

X^{1a} represents -O-;

R^{2a} is selected from one of the following three groups:

- 1) C₁₋₅alkylR^{3a} (wherein R^{3a} is as defined herein before in formula II);
 - 5 2) C₂₋₅alkenylR^{3a} (wherein R^{3a} is as defined herein before in formula II);
 - 3) C₂₋₅alkynylR^{3a} (wherein R^{3a} is as defined herein before in formula II);
- or a pharmaceutically acceptable salt, solvate or prodrug thereof.

A particularly preferred VEGF receptor tyrosine kinase inhibitor may be selected from:

- 10 4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline,
4-(2-fluoro-4-methylanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline,
4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline,
4-(4-chloro-2,6-difluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline,
4-(4-bromo-2,6-difluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline,
- 15 4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(piperidin-4-ylmethoxy)quinazoline,
4-(2-fluoro-4-methylanilino)-6-methoxy-7-(piperidin-4-ylmethoxy)quinazoline,
4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(piperidin-4-ylmethoxy)quinazoline,
4-(4-chloro-2,6-difluoroanilino)-6-methoxy-7-(piperidin-4-ylmethoxy)quinazoline,
4-(4-bromo-2,6-difluoroanilino)-6-methoxy-7-(piperidin-4-ylmethoxy)quinazoline,
- 20 and salts, prodrugs or solvates thereof especially hydrochloride salts thereof.

A further particularly preferred VEGF receptor tyrosine kinase inhibitor is
6-methoxy-4-(2-methylindol-5-yloxy)-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline, and
and salts, prodrugs or solvates thereof especially hydrochloride salts thereof.

- A further particularly preferred antiangiogenic agent is
- 25 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(2-(1,2,3-triazol-1-yl)ethoxy)quinazoline
and salts, prodrugs or solvates thereof especially hydrochloride salts thereof.

An especially preferred antiangiogenic agent is:
4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline,
and salts, prodrugs or solvates thereof especially hydrochloride salts thereof.

It is also to be understood that certain compounds of the formula I, formula II and formula III and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which inhibit VEGF receptor tyrosine kinase activity.

5 Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

- a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);
- b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard
- 10 p. 113-191 (1991);
- c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);
- d) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and
- e) N. Kakeya, *et al.*, Chem Pharm Bull, 32, 692 (1984).

15 An *in vivo* hydrolysable ester of a compound of the formula I, formula II or formula III containing carboxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid, for example, a pharmaceutically acceptable ester formed with a (1-6C)alcohol such as methanol, ethanol, ethylene glycol, propanol or butanol, or with a phenol or benzyl alcohol such as phenol or

20 benzyl alcohol or a substituted phenol or benzyl alcohol wherein the substituent is, for example, a halo (such as fluoro or chloro), (1-4C)alkyl (such as methyl) or (1-4C)alkoxy (such as ethoxy) group. The term also includes α -acyloxyalkyl esters and related compounds which breakdown to give the parent hydroxy group. Examples of α -acyloxyalkyl esters include acetoxymethoxycarbonyl and 2,2-dimethylpropionyloxymethoxycarbonyl.

25 An *in vivo* hydrolysable ester of a compound of the formula I, formula II or formula III containing a hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent alcohol. The term includes inorganic esters such as phosphate esters and α -acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the

30 parent hydroxy group. Examples of α -acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in vivo* hydrolysable ester forming groups for

hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxy carbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

- 5 A suitable value for an *in vivo* hydrolysable amide of a compound of the formula I containing a carboxy group is, for example, a N-(1-6C)alkyl or N,N-di-(1-6C)alkyl amide such as N-methyl, N-ethyl, N-propyl, N,N-dimethyl, N-ethyl-N-methyl or N,N-diethyl amide.

- A suitable pharmaceutically-acceptable salt of a compound of the formula I,
10 formula II or formula III is, for example, an acid-addition salt of a compound of the formula I, formula II or formula III which is sufficiently basic, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid; or, for example a salt of a compound of the formula (I) which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a calcium or
15 magnesium salt, or an ammonium salt, or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

The antiangiogenics described herein may be made by standard techniques including those described in the patent applications described hereinbefore which are incorporated herein by reference.

- 20 The invention will now be illustrated by the following non-limiting example and with reference to the accompanying figure.

Figure 1 shows the effect of a VEGF receptor tyrosine kinase inhibitor [4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline] on the diastolic blood pressure in rats.

25

Example 1

Measurement of blood pressure in conscious rats by radio telemetry

- Blood pressure was measured using the Data Sciences radio-telemetry equipment (Data Sciences International, Saint Paul, Minnesota, USA). This provides a means of
30 measuring the blood pressure (BP), heart rate and activity of a conscious unrestrained rat remotely. The measurements obtained using this system are free from the stresses induced

by surgery and restraint. The system comprises a pressure transducer (TA11PA-C40) (the 'implant') implanted in the abdomen of a rat which transmits a radio signal indicating the pressure in the aorta of the animal. The signal is detected by a receiver (RA1010) placed under the plastic cage which houses the animal. The signal is evaluated and recorded
5 automatically by pre-written computer software (DataQuest IV installed on an IBM-compatible personal computer, containing an Intel™ 486 processor).

Implantation Methodology

Rats were anaesthetised with "Fluothane™" inhalation anaesthetic. The abdomen of
10 the rat was shaved and the skin coated with a topical disinfectant. An incision was made in the outer skin to expose the abdominal muscle wall which was cut along the mid-line and opened. The viscera of the animal was held back with retractors and the abdominal aorta located. The aorta was cleaned of connective tissue over a 2-3 cm length and carefully separated from the associated vena cava. Care was taken to ensure the area of aorta prepared
15 was below the renal arteries to avoid any potential occlusion of the kidneys following surgery.

A tie was placed loosely under the aorta which was then lifted to occlude the vessel. A puncture was made into the vessel using a 21 gauge needle (Micro Lance, Becton Dickinson) the tip of which had previously been bent to approximately 90 degrees to the
20 needle shaft. Using the bevel of the needle (held in place in the vessel) the tip of the 'implant' catheter was carefully inserted into the vessel. After withdrawal of the needle tip a small drop of surgical glue (Vet Bond 3M) was run down the catheter to form a seal between the catheter and the blood vessel.

The 'implant' was coated with fine mesh which was used to stitch the implant body
25 to the inside of the abdominal wall. The abdominal muscle wall was closed with absorbable stitches. The ends of the stitches were trimmed and the outer skin of the animal was closed using surgical autoclips. These autoclips were removed 7 days after surgery.

General Study Protocol

Male wistar rats were implanted (as described above). Following removal of surgical autoclips all rats were handled daily to acclimatise them to dosing techniques. The animals were then dosed with vehicle (1% polysorbate in water) for a further week.

- 5 Blood pressure data was recorded from each animal every 10 minutes throughout the study. The animals were housed in a facility using a 12 hour cycle of light and dark. Normal rat behaviour was seen during the study i.e. the animals rested during the light phase and were active during the dark phase. To obtain more reproducible basal measurements all data reported was obtained during the 12 hour light phase when the test animals were inactive.
- 10 This average day time blood pressure measurement for each rat was calculated over a 4 day period immediately prior to the commencement of compound dosing.

- 4-(4-Bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline, was dosed p.o. at 12.5 mg/kg once daily for 10 days. For the next 4 days (i.e. days 11 to 14 of compound dosing) the rats were dosed with the ACE inhibitor
- 15 captopril at 30 mg/kg p.o. once daily in addition to the quinazoline compound. The average blood pressure of each rat was calculated daily and the difference between the daily calculated pressure and the starting pressure was expressed.

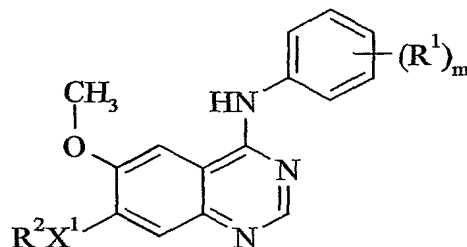
- Figure 1 shows the effect of the VEGF receptor tyrosine kinase inhibitor [4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline] on
- 20 the diastolic blood pressure in rats. The increase in blood pressure is reversed by the addition of an ACE inhibitor, captopril. Data are presented for a control rat and 3 different rats dosed with the VEGF tyrosine kinase inhibitor.

CLAIMS

1. Use of a combination of an anti-angiogenic agent and an anti-hypertensive agent for use in the manufacture of a medicament for the treatment of a disease state associated with angiogenesis in a warm-blooded mammal, such as a human being.
2. Use according to claim 1 wherein the anti-angiogenic agent affects the level of nitric oxide.
3. Use according to claim 1 wherein the anti-angiogenic agent is a VEGF receptor tyrosine kinase inhibitor.
4. Use according to claim 3 wherein the anti-angiogenic agent is selected from:
6-methoxy-4-(2-methylindol-5-yloxy)-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline,
4-(4-fluoroindol-5-yloxy)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline,
4-(4-fluoroindol-5-yloxy)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline,
4-(6-fluoroindol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline,
4-(4-fluoroindol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline,
4-(4-fluoroindol-5-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,
4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline,
4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,
4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline,
4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline,
4-(4-fluoroindol-5-yloxy)-6-methoxy-7-(2-(1-methylpiperidin-4-yl)ethoxy)quinazoline,
(2R)-7-(2-hydroxy-3-(pyrrolidin-1-yl)propoxy)-4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxyquinazoline, and
4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(2-(1-methylpiperidin-4-yl)ethoxy)quinazoline;
or a pharmaceutically acceptable salt thereof.

-32-

5. Use according to claim 3 wherein the anti-angiogenic agent is a compound of the formula II:



5

formula (II)

[wherein:

m is an integer from 1 to 3;

R¹ represents halogeno or C₁₋₃alkyl;

X¹ represents -O-;

10 R² is selected from one of the following three groups:

1) C₁₋₅alkylR^{3a} (wherein R^{3a} is piperidin-4-yl which may bear one or two substituents selected from hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl and C₁₋₄alkoxy;

2) C₂₋₅alkenylR^{3a} (wherein R^{3a} is as defined hereinbefore);

3) C₂₋₅alkynylR^{3a} (wherein R^{3a} is as defined hereinbefore);

15 and wherein any alkyl, alkenyl or alkynyl group may bear one or more substituents selected from hydroxy, halogeno and amino;
or a pharmaceutically acceptable salt thereof.

6. Use according to any one of claims 1, 2, 3 and 5 wherein the anti-angiogenic agent is

20 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline or a pharmaceutically acceptable salt thereof.

7. Use according to any one of the preceding claims wherein the anti-hypertensive agent is an ACE inhibitor.

25

8. Use according to claim 7 wherein the anti-hypertensive agent is lisinopril.

9. A pharmaceutical composition, comprising:
- a) an anti-angiogenic agent or a pharmaceutically acceptable salt, solvate or pro-drug thereof;
 - b) an anti-hypertensive agent or a pharmaceutically acceptable salt, solvate or pro-drug thereof; and optionally
- 5 c) a pharmaceutically acceptable carrier or diluent.
10. A kit, for use in producing an anti-angiogenic effect and/or vascular permeability reducing effect in a warm-blooded animal such as a human being, comprising:
- a) an anti-angiogenic agent or a pharmaceutically acceptable salt, solvate or pro-drug thereof
- 10 or a pharmaceutical composition thereof;
- b) an anti-hypertensive or a pharmaceutically acceptable salt, solvate or pro-drug thereof or a pharmaceutical composition thereof; and
 - c) a container means for containing said agents.
- 15 11. A method of treatment of a disease state associated with angiogenesis which comprises the administration of an effective amount of a combination of an anti-angiogenic agent and an anti-hypertensive agent to a warm-blooded animal, such as a human being.

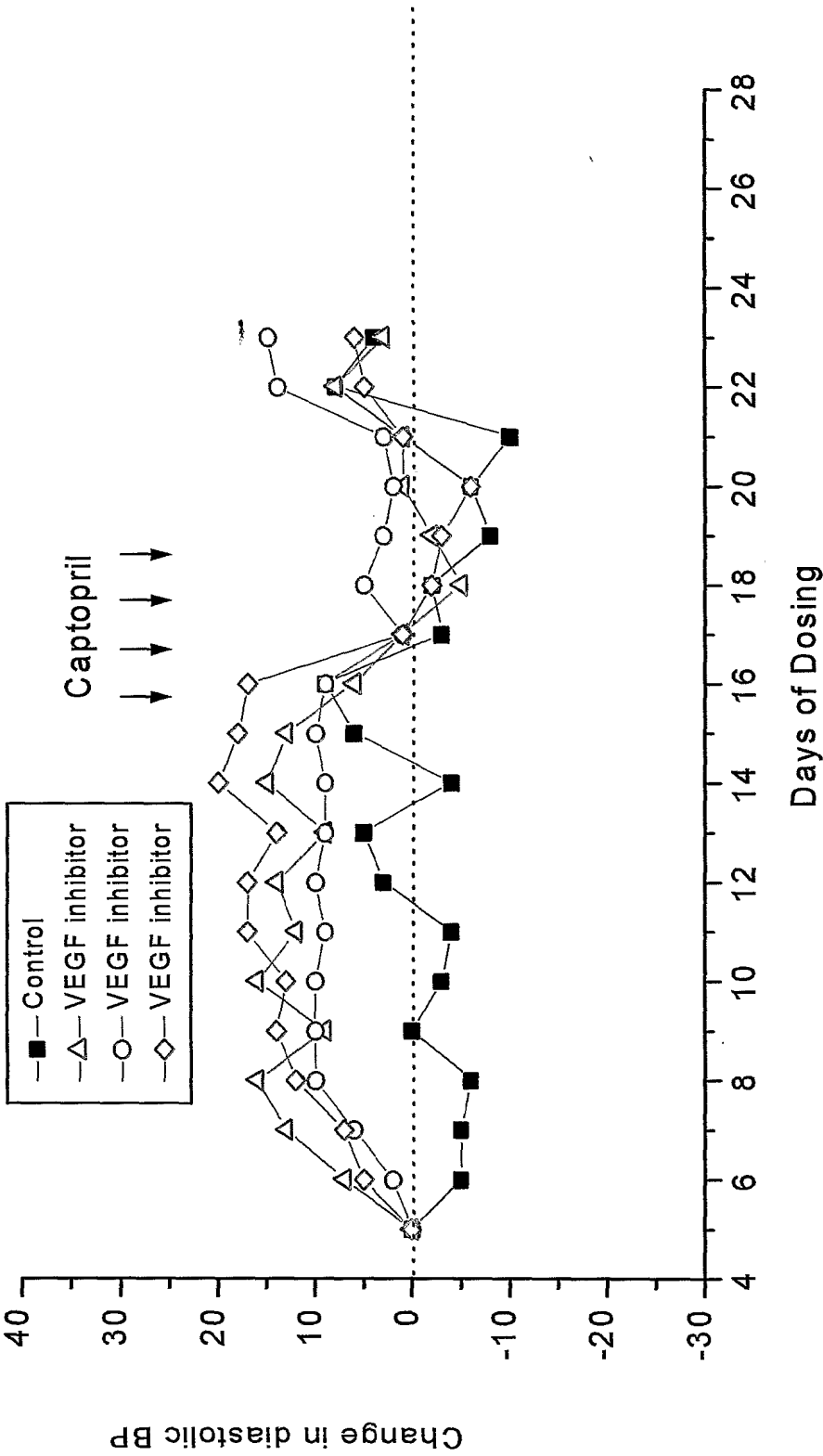


Figure 1

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 01/01522

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/505 A61K31/40 A61P5/50 A61P9/00 A61P17/06
 A61P29/00 A61P27/00 A61P35/00 A61P37/00 A61P43/00
 //(A61K31/505,31:40)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, MEDLINE, EMBASE, BIOSIS, CANCERLIT, AIDSLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 646 136 A (PETROW VLADIMIR ET AL) 8 July 1997 (1997-07-08) abstract column 2, line 15 - column 3, line 13 column 4, line 16 - line 32 column 17, line 66 - column 18, line 20 column 18, line 44 - line 46 column 19, line 19 - line 22 claim 12	4-8
P, A	WO 00 47212 A (PLE PATRICK ;HENNEQUIN LAURENT FRANCOIS AND (FR); ZENECA PHARMA SA) 17 August 2000 (2000-08-17) cited in the application abstract page 1, line 3 - line 8 page 2, line 15 - line 31 claims 1-22	4-8



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

2 August 2001

Date of mailing of the international search report

13/08/2001

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 01/01522

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, A	US 6 191 144 B1 (ISNER JEFFREY MICHAEL) 20 February 2001 (2001-02-20) abstract column 1, line 8 - line 23 column 2, line 61 - column 3, line 5 column 3, line 26 - line 38 column 14, line 33 - line 49 claims 1-17 -----	4-8

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-3,9-11

Present claims 1-3 and 11 relate to an extremely large number of disease states. In fact, the expression "a disease state associated with angiogenesis" not only encompasses diseases caused by angiogenesis, but also those present at the same time as angiogenesis. A lack of clarity (and/or conciseness) within the meaning of Art. 6 PCT therefore arises to such an extent as to render a meaningful search of the claims impossible.

Independent of the above, the Applicant has not provided any test to demonstrate whether a disease is associated with angiogenesis or not. There is therefore insufficient disclosure (Art. 5 PCT) to allow the skilled man to determine which diseases fall within the definition.

The definition of the disease state as being "associated with angiogenesis" is furthermore considered to employ unusual parameters (cf. PCT Guidelines C-IV, 7.5). The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Art. 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible.

Notwithstanding these objections, present claims 1-3 and 9-11 relate to an extremely large number of possible products. Support within the meaning of Art. 6 PCT and disclosure within the meaning of Art. 5 PCT is to be found, however, for only a very small proportion of the products claimed. Thus, a vast range of anti-hypertensives is claimed, yet only one example of the use of an ACE inhibitor is given. Similarly, an overly extensive range of anti-angiogenic agents is claimed, whereas the one solitary example presented in the example employs a quinazoline falling within Formula (II) according to claim 5. The claims therefore lack support, and the application lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search has been carried out for those parts of the application which do appear to be clear and sufficiently supported, namely

the use of a combination of

- (a) an antiangiogenic agent as defined in claim 5; and,
- (b) an ACE inhibitor (claim 7)

for the preparation of a medicament for the treatment of

those disease states disclosed in the description on page 1, line 29 to page 2, line 3.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 01/01522

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5646136 A	08-07-1997	AU 696678 B	17-09-1998
		AU 1598895 A	01-08-1995
		CA 2180325 A	13-07-1995
		EP 0742718 A	20-11-1996
		JP 9511485 T	18-11-1997
		WO 9518621 A	13-07-1995
WO 0047212 A	17-08-2000	AU 2447500 A	29-08-2000
US 6191144 B	20-02-2001	NONE	